

What is claimed is:

1. A method of detecting dimers of membrane-associated analytes in a cell membrane, the method comprising the steps of:
  - 5 providing a binding compound specific for a first membrane-associated analyte of a dimer, the dimer comprising the first membrane-associated analyte and a second membrane-bound analyte, and the binding compound having one or more molecular tags each attached thereto by a cleavable linkage, the one or more molecular tags each having a separation characteristic;
  - 10 providing a cleaving probe specific for the second membrane-bound analyte, the cleaving probe having a cleavage-inducing moiety with an effective proximity;
  - 15 mixing the cleaving probe, the binding compound, and the cell membrane such that the cleaving probe specifically binds to the first membrane-associated analyte and the binding compound specifically binds to the second membrane-associated analyte and such that cleavable linkages of the binding compound are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and
  - separating and identifying the released molecular tags to determine the presence or absence or the amount of dimer in the cell membrane.
2. The method of claim 1 wherein said first membrane-associated analyte and said second membrane associated analyte are each receptors in said cell membrane and said separation characteristic of said one or more molecular tags is electrophoretic mobility.
3. The method of claim 2 wherein said step of separating and detecting further includes electrophoretically separating said released molecular tags in a separation buffer.
- 25 4. The method of claim 2 wherein said cleavage-inducing moiety of said cleaving probe is a photosensitizer and wherein said cleaving probe and said binding compound each comprise an antibody binding composition.
- 30 5. The method of claim 4 wherein said cell surface receptors are selected from the group consisting of epidermal growth factor receptors and G-protein coupled receptors.

6. The method of claim 5 wherein said cell surface receptors are selected from the group consisting of Her1, Her2, Her3, and Her4.

7. A method of detecting a dimer of a first membrane-associated analyte and a second membrane-associated analyte in a cell membrane, the method comprising the steps of:

5 providing one or more binding compounds specific for different antigenic determinants of the dimer, each binding compound having one or more molecular tags each attached thereto by a cleavable linkage, and the molecular tags of different binding compounds having different separation characteristics;

10 providing a cleaving probe specific for an antigenic determinant of the dimer different from the antigenic determinants that the one or more binding compounds are specific for, the cleaving probe having a cleavage-inducing moiety with an effective proximity;

15 mixing the cleaving probe, the one or more binding compounds, and the cell membrane such that the cleaving probe and the one or more binding compounds specifically bind to their respective antigenic determinants and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of dimer in the cell membrane.

20 8. The method of claim 7 wherein said first membrane-associated analyte and said second membrane associated analyte are each cell surface receptors and wherein at least one of said one or more binding compounds is specific for a phosphorylation site of said dimer.

25 9. The method of claim 8 wherein said separation characteristics are electrophoretic mobilities and said step of separating and identifying includes electrophoretically separating said released molecular tags to form distinct peaks in an electropherogram.

10. The method according to claims 7, 8, or 9 wherein said first membrane-associated analyte and said second membrane-associated analyte are each selected from the group consisting of epidermal growth factor receptors and G-protein coupled receptors.

30 11. The method of claim 10 wherein said first membrane-associated analyte and said second membrane-associated analyte are each selected from the group consisting of Her1, Her2, Her3, and Her4.

12. The method of claim 11 wherein said dimer is a heterodimer and wherein each of said cleaving probe and one or more binding compounds comprise an antibody binding composition.

5 13. The method of claim 12 wherein said heterodimer comprises Her2 and Her3.

14. The method of claim 11 wherein said dimer is a homodimer of Her1 and wherein each of said cleaving probe and one or more binding compounds comprise an antibody binding composition.

10 15. A method of detecting oligomerization of a plurality of receptor types in a cell membrane, the method comprising the steps of:  
providing a cleaving probe specific for a first receptor type of the plurality, the cleaving probe having a cleavage-inducing moiety with an effective proximity;  
providing one or more binding compounds each specific for a different second receptor type of the plurality, each binding compound having one or more molecular tags each attached thereto by a cleavable linkage, and the molecular tags of different binding compounds having different separation characteristics;  
mixing the cleaving probe, the one or more binding compounds, and the cell membrane such that the cleaving probe and the one or more binding compounds specifically bind to their respective receptors and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing moiety so that molecular tags are released; and  
separating and identifying the released molecular tags to determine the presence or absence or the amount of oligomerization of the receptor types in the cell membrane.

20 25 16. The method of claim 15 wherein said separation characteristics are electrophoretic mobilities and said step of separating and identifying includes electrophoretically separating said released molecular tags to form distinct peaks in an electropherogram.

30 17. The method of claim 16 wherein said cleavage-inducing moiety of said cleaving probe is a photosensitizer.

18. The method of claim 17 wherein said first receptor type and said second receptor type are selected from the group consisting of epidermal growth factor receptors and G-protein coupled receptors.

5 19. A method of detecting a dimer comprising a first receptor type and a second receptor type in a biological sample, the method comprising the steps of:

providing one or more binding compounds specific for different antigenic determinants of the dimer, each binding compound having one or more molecular tags each attached thereto by a cleavable linkage, and molecular tags of different binding compounds having different separation  
10 characteristic such that distinct peaks are formed in a separation profile upon separation;

providing a cleaving probe having a cleavage-inducing moiety with an effective proximity, the cleaving probe being specific for an antigenic determinant of the dimer different from the antigenic determinants for the one or more binding compounds, with the proviso that at least one of said antigenic determinants is on the first receptor type and at least one of said antigenic determinants is on the second receptor type;

15 forming an assay mixture comprising the cleaving probe, the one or more binding compounds, and the biological sample such that the cleaving probe and the one or more binding compounds specifically bind to their respective antigenic determinants and the cleavable linkages of the one or more binding compounds are within the effective proximity of the cleavage-inducing  
20 moiety so that molecular tags are released; and

separating and identifying the released molecular tags to determine the presence or absence or the amount of dimer in the biological sample.

20. The method of claim 19 wherein said separation characteristic is electrophoretic mobility  
25 and said step of separating and identifying includes electrophoretically separating said released molecular tags to form distinct peaks in an electropherogram.

21. The method of claim 20 wherein said step of forming includes the steps of incubating said cleaving probe, said one or more binding compounds, and said biological sample in a binding buffer,  
30 and exchanging the binding buffer with a separation buffer prior to said separating of said released molecular tags.

22. The method of claim 20 wherein said cleavage-inducing moiety is a sensitizer and wherein said step of forming includes inducing said sensitizer to generate an active species that cleaves said cleavable linkages within said effective proximity thereof.

5 23. The method of claim 22 wherein said sensitizer is a photosensitizer and wherein said active species is singlet oxygen.

24. The method of claim 20 wherein said cleaving probe and said one or more binding compounds each comprise an antibody binding composition.

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25 The method of claim 20 wherein at least one of said antigenic determinants is a phosphorylation site of said first receptor type or said second receptor type.

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26. The method according to claims 19, 20, 21, 22, 23, 25, or 25 wherein said first receptor type and said second receptor type are selected from the group consisting of epidermal growth factor receptors and G-protein coupled receptors.

27. The method of claim 26 wherein said one or more binding compounds are a plurality of binding compounds in the range of from 2 to 10.

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28. The method of claim 27 wherein said first receptor type and said second receptor type are each selected from the group consisting of Her1, Her2, Her3, and Her4.

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29. The method of claim 28 wherein said dimer is a heterodimer or homodimer comprising receptor types selected from the group consisting of Her1, Her2, Her3, and Her4.

30. The method of claim 29 wherein said dimer is a Her1-Her1 homodimer, a Her1-Her2 heterodimer, a Her1-Her3 heterodimer, or a Her2-Her3 heterodimer.

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